

### **Remarks**

An Office Action was mailed in the above-captioned application on June 2, 2006. Claims 1-24 were pending. Claims 1-20 and 24 were rejected. Claims 21-23 were withdrawn from consideration. Claims 1, 11, 17 and 18 were objected to. This Amendment and Remarks document is submitted in response to said Office Action. Applicants respectfully request reconsideration of the application, withdrawal of all rejections, and allowance of the application in view of the amendments and remarks below.

#### **Restriction Requirement**

A restriction requirement was made with respect to pending claims 1-24. The Examiner placed the inventions into two groups:

Group I. Claims 1-20 and 24, drawn to a method of treating pain comprising the administration of a compound selected from the group consisting of loxapine, pharmaceutically acceptable salts of loxapine, and loxapine prodrugs, classified in class 514, subclass 185.

Group II. Claims 21-23, drawn to a composition comprising (a) an analgesic selected from a group consisting of loxapine, pharmaceutically acceptable drugs thereof, and loxapine prodrugs and (b) a pharmaceutically acceptable carrier, classified in class 424, subclasses 43-45, depending upon the carrier selected.

In response to this restriction/election requirement, Applicants hereby elect Group I, Claims 1-20 and 24. Applicants make this election without traverse.

#### **Objection to the Specification**

The Examiner has objected to the specification, requiring Applicants to amend the disclosure to include the material incorporated by reference, if the material is relied upon to overcome any objection, rejection, or other requirement imposed by the Office. Office Action at 4. The Examiner has not asserted what essential material is lacking in the present specification. Applicants believe that all essential material has been disclosed in the present application. Reconsideration or clarification is respectfully requested regarding essential material which has not been disclosed in the present specification.

### The Amendments to the Claims

The Applicants have amended Claims 1, 10, 11, 17 and 18. The claims were amended to correct minor grammatical errors identified by the Examiner. The amendments to the claims do not introduce new matter.

### Claim Rejections under 35 U.S.C. §102

The Examiner has rejected claims 1-3 and 10-15 under 35 U.S.C. 102(e) as being anticipated by Dehaven et al. (WO 02/060870). The Examiner states that Dehaven et al. “discloses in claims 1 and 3 methods of inducing analgesia in a patient comprising administration of compounds of formula (I) and (Ib), both of which encompass loxapine.” Office Action at 6.

Applicants respectfully disagree. Dehaven et al. repeatedly states that N-desmethyl analogs of clozapine and loxapine (*i.e.*, N-desmethylozapine and amoxapine, respectively) constitute preferred embodiments. *See, e.g.*, Dehaven et al. at 12, lines 16-18. Dehaven et al. also states that phenothiazines, thioxanthenes, and related tricyclic compounds of general formula (I) “may also have  $\delta$  opioid receptor agonist activity, and therefore fall within the scope of the present invention.” *Id.* at 12, lines 19-21.

Table 1 of Dehaven et al., entitled “N-desmethylozapine is a potent, selective inhibitor of [ $^3$ H]dinprenorphine binding to the human  $\delta$  opioid receptor,” compares clozapine and loxapine to their respective N-desmethyl analogs. *Id.* at 23. Table 1 lists the  $K_i$ (nM) or % inhibition at 10 $\mu$ M as indicators of the compounds. The preferred embodiment N-desmethylozapine yields a  $K_i$  for the  $\delta$  opioid receptor of 24 nM while, in comparison, clozapine yields as the much higher value of 928 nM (indicating poor affinity of clozapine for the  $\delta$  opioid receptor). Similarly, the preferred embodiment amoxapine (N-desmethyl derivative of loxapine) yields a  $K_i$  for the  $\delta$  opioid receptor of 279 nM while, in comparison, loxapine provides only 26% inhibition at a concentration 10  $\mu$ M (which is orders of magnitude higher in dose than the amoxapine, indicating poor affinity of loxapine for the  $\delta$  opioid receptor). Dehaven et al. thus uses clozapine and loxapine as negative controls in comparison to the stated preferred embodiments of N-desmethylozapine and amoxapine.

After the poor results in the *in vitro* opioid receptor binding assays, Dehaven et al. does not use loxapine in any of the *in vivo* studies. Thus, Dehaven et al. does not administer loxapine

to a subject to treat pain or teach administering loxapine to a subject to treat pain. Rather, Dehaven et al. teaches away from using loxapine as an analgesic because loxapine does not have the requisite  $\delta$  opioid receptor agonist activity.

The Court of Appeals for the Federal Circuit has stated that anticipation requires the presence in a single prior art reference each and every element of the claimed invention. *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1458 (Fed. Cir. 1984); *Alco Standard Corp. v. Tennessee Valley Auth.*, 1 U.S.P.Q.2d 1337, 1341 (Fed. Cir. 1986). "There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention." *Scripps Clinic v. Genentech Inc.*, 18 U.S.P.Q.2d 1001, 1010 (Fed. Cir. 1991) (citations omitted).

Dehaven et al. does not teach a method for treating pain in a subject comprising administering to said subject an effective amount of a compound selected from the group consisting of loxapine, pharmaceutically acceptable salts of loxapine, and prodrugs of loxapine. In fact, Dehaven et al. teaches away from use of loxapine for treating pain. Accordingly, the present invention is not anticipated by Dehaven et al. and reconsideration is respectfully requested.

#### Rejection under 35 U.S.C. §103

The Examiner has rejected claims 1-9 and 24 as being unpatentable over Burns et al. The Examiner states "[i]t would have been apparent to a person of ordinary skill in the art at the time of the instant invention that one could utilize Burn's inhalation device to deliver loxapine hydrochloride in the practice of a method of treating pain, because loxapine hydrochloride is a known headache analgesic." Office Action at 9. However, at the time of the invention, loxapine hydrochloride was not a known headache analgesic. The Examiner points to the specification at column 7 lines 10-17 as evidence that loxapine hydrochloride was a known headache analgesic; however, these lines merely list a variety of drug classes and a variety of drugs – they do not indicate that loxapine hydrochloride was used as a headache analgesic. Burns et al. reads:

"For example, with neuroleptics, psychotropics, narcotic antagonists, other central nervous system (CNS) drugs and headache analgesics, such as prochlorperazine, fluphenazine hydrochloride, chlorpromazine, trifluoperazine hydrochloride, thioridazine hydrochloride, loxapine hydrochloride, and haloperidol decanoate."

It is inappropriate to read this sentence to mean that each drug listed belongs to each of the drug classes listed. This arbitrary grouping together of these drug classes does not disclose that loxapine hydrochloride is a headache analgesic.

According to the MPEP § 2143, “to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art references (or references when combined) must teach or suggest all the claim limitations.” Obviousness cannot be established by combining teachings in the prior art, absent some teaching or suggestion in the prior art that the combination be made (*In re Stencel* 828 F. 2d 751, 4 USPQ2d 1071 (Fed. Cir. 1987); *In re Newell* 891 F. 2d 899, 13 USPQ2d 1248 (Fed. Cir. 1989)).

Burns et al. fails to teach or suggest loxapine hydrochloride for use as an analgesic. Thus, the Office Action fails to establish even a *prima facie* case of obviousness as each and every element of claims 1-9 and 24 is not taught or disclosed by Burns et al.

The Examiner has rejected claims 10-15 as being unpatentable over Burns et al. in further view of Drug Information Handbook, 2<sup>nd</sup> edition. As discussed above, Burns et al. fails to disclose the use of loxapine hydrochloride for use as an analgesic. Drug Information Handbook, 2<sup>nd</sup> edition does not overcome this deficiency. In fact, the Drug Information Handbook, 2<sup>nd</sup> edition, indicates that loxapine is used for the treatment of psychotic disorders, giving no indication that the drug could be used in the treatment of pain. Drug Information Handbook, 2<sup>nd</sup> edition, page 554. Thus, the Examiner has not established a *prima facie* case of obviousness.

The Examiner has rejected claims 16-17 and 19-20 as being unpatentable over Burns et al. in view of Nguyen et al. As discussed above, Burns et al. fails to disclose the use of loxapine hydrochloride for use as an analgesic. Nguyen does not overcome this deficiency. Nguyen discloses loxapine in its known role as an anxiolytic, but not as an analgesic. Because Nguyen fails to overcome the deficiencies of Burns et al., the Examiner has not established a *prima facie* case of obviousness.

The Examiner has rejected claims 16-18 as being unpatentable over Burns et al. in further view of Rabinowitz et al. As discussed above, Burns et al. fails to disclose the use of loxapine hydrochloride for use as an analgesic. Rabinowitz et al. does not overcome this deficiency. Because Rabinowitz fails to overcome the deficiencies of Burns et al., the Examiner has not established a *prima facie* case of obviousness.

Reconsideration is respectfully requested.

#### The Double Patenting Rejection.

Claims 1, 16-17, and 19 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 7, 9, 10, 12 and 13 of U.S. Patent No. 6,716,416.

Claims 1 and 16-20 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 12, 15, 16 and 18 of copending Application No 10/653,876 and claims 1 and 7-9 of copending Application No. 10/633,877.

An obviousness-type double patenting rejection is appropriate when a claim merely defines an obvious variation of an invention claimed in a patent. MPEP § 804(II)(B)(1). A double-patenting rejection must rely on a comparison with the claims in an issued or to be issued patent. MPEP § 804(III).

Once the scope of the claims has been determined, Applicants agree to file the appropriate terminal disclaimers.

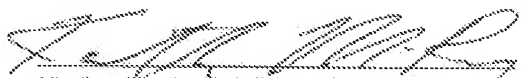
#### Closing Remarks

Applicants believe that the pending claims are in condition for allowance. If it would be helpful to obtain favorable consideration of this case, the Examiner is encouraged to call and discuss this case with the undersigned.

This constitutes a request for any needed extension of time and an authorization to charge all fees therefore to deposit account No. 19-5117, if not otherwise specifically requested. The undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to be charged to deposit account No. 19-5117.

Respectfully submitted,

Date 11/29/06



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